UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

UNITED STATES OF AMERICA	)	
	)	
Plaintiff,	)	
	)	No. _____
v.	)	
	)	
ELI LILLY AND COMPANY	)	
	)	
Defendant.	)	

COMPLAINT FOR PERMANENT INJUNCTION

The United States of America, Plaintiff, by Timothy M. Morrison, Acting United States Attorney for the Southern District of Indiana, respectfully represents to this Honorable Court as follows:

STATUTORY VIOLATIONS

1. This statutory injunction proceeding is brought under the Federal Food, Drug, and Cosmetic Act (the "FDCA"), 21 U.S.C. § 301 et seq., to permanently enjoin defendant ELI LILLY AND COMPANY ("ELI LILLY" or "Defendant"), from:

a. violating the FDCA, 21 U.S.C. § 331(a), by directly or indirectly causing the introduction or delivery for introduction into interstate commerce of Evista, a human drug within the meaning of 21 U.S.C. § 321(g), that is misbranded within the meaning of 21 U.S.C. § 352(f)(1), in that the labeling of the drug does not bear adequate directions for use in preventing or reducing the risk of breast cancer, reducing the risk of cardiovascular disease, or for any other unapproved use, unless and until it has been authorized to do so by the United States Food and

Drug Administration ("FDA") by the approval of a supplement to the New Drug Application ("NDA") for Evista;

b. violating the FDCA, 21 U.S.C. § 331(k), by directly or indirectly causing Evista, a human drug within the meaning of 21 U.S.C. § 321(g), to be misbranded within the meaning of 21 U.S.C. § 352(f)(1), in that the labeling of the drug does not bear adequate directions for use in preventing or reducing the risk of breast cancer, reducing the risk of cardiovascular disease, or for any other unapproved use, while such drug is held for sale after shipment of it or any of its components in interstate commerce, unless and until it has been authorized to do so by the FDA by the approval of a supplement to the NDA for Evista; and

c. directly or indirectly promoting Evista for use in preventing or reducing the risk of breast cancer, reducing the risk of cardiovascular disease, or for any other unapproved use in a manner that violates the FDCA, 21 U.S.C. § 301 et seq., unless and until it has been authorized to do so by the FDA by the approval of a supplement to the NDA for Evista.

JURISDICTION

2. This Court has jurisdiction over this action and the parties under 28 U.S.C. §§ 1331, 1337, and 1345, and 21 U.S.C. § 332(a).

3. Venue in this district is proper under 28 U.S.C. §§ 1391(b) and (c).

DEFENDANT

4. ELI LILLY is a corporation operating and existing under the laws of the State of Indiana, with headquarters and manufacturing facilities located in Indianapolis, Indiana, within the Southern District of Indiana. ELI LILLY is engaged in the development, manufacture, promotion, sale, and interstate distribution of pharmaceutical drugs intended for human use. ELI

LILLY distributes pharmaceutical drugs or directs the distribution of pharmaceutical drugs from the Southern District of Indiana to all fifty states, the District of Columbia, and all United States Territories.

THE FEDERAL FOOD, DRUG AND COSMETIC ACT

5. The FDCA, *inter alia*, governs the interstate distribution of drugs for human use as codified in Title 21, United States Code, Section 301 et seq. The FDCA, and its implementing regulations, requires that before a new drug may legally be distributed in interstate commerce, a sponsor of a new drug must receive approval of an application submitted pursuant to 21 U.S.C. § 355.

6. The FDCA requires, at 21 U.S.C. § 355(b), that the sponsor of an NDA submit to the FDA, as part of the NDA, labeling for all proposed intended uses for the drug which includes, among other things, the conditions for therapeutic use. The NDA must also provide, to the satisfaction of FDA, data generated in randomized and well-controlled clinical trials that demonstrate that the drug will be safe and effective when used in accordance with the proposed labeling.

7. The FDCA, at 21 U.S.C. § 355(a), prohibits the introduction into interstate commerce of any new drug, unless an approval of an application is effective. Only after the application, including the proposed labeling, has been reviewed and approved by the FDA, is the sponsor permitted by law to promote and market the drug, and only for the medical conditions of use specified in the approved labeling, for which use FDA has found sufficient evidence of safety and effectiveness. Uses not approved by FDA, and not included in the drug's approved labeling, are known as unapproved uses or off-label uses.

8. The FDCA, and the regulations promulgated thereunder, requires that in order to label or promote a drug for a use different than the conditions for use specified in the approved labeling, the sponsor must submit the newly proposed indications for use and evidence, in the form of randomized and well-controlled clinical studies, sufficient to demonstrate that the drug is safe and effective for the newly proposed therapeutic use or uses. Only upon receiving approval from the FDA can the sponsor label or promote the drug for the new intended use or uses.

9. The FDCA, at 21 U.S.C. § 352(f)(1), provides that a drug is misbranded if, among other things, the labeling does not bear adequate directions for use. Adequate directions for use cannot be written for medical indications or uses for which the drug has not been proven to be safe and effective through well-controlled clinical studies.

10. The FDCA, 21 U.S.C. § 331(a), prohibits the distribution in interstate commerce of a misbranded drug.

11. On or about June 8, 1997, ELI LILLY submitted an NDA seeking approval of a drug called Evista (also known by the chemical name raloxifene hydrochloride), which was a new drug within the meaning of 21 U.S.C. § 321(p) and 21 C.F.R. § 310.3(h)(4) and (5). In that application, ELI LILLY sought to demonstrate the drug's safety and efficacy for, and sought approval for, use of Evista as therapy for the prevention of osteoporosis in postmenopausal women. In its application, ELI LILLY also sought approval for language in the "Indications and Usage" section of the label that "there was a statistically significant reduction in the frequency of newly diagnosed breast cancer in raloxifene-treated women compared to placebo."

12. On or about September 25, 1997, ELI LILLY was informed by the FDA, in response to ELI LILLY's NDA proposal to include language in the product label with respect to

newly diagnosed breast cancer that: "[i]n reviewing the proposed label for raloxifene as an agent that is indicated for the prevention of osteoporosis, it is not acceptable to include language elsewhere in the label that 'there was a statistically significant reduction in the frequency of newly diagnosed breast cancer in raloxifene-treated women compared to placebo.' Acceptance of this claim would effectively provide the sponsor with a second indication for raloxifene without review by the Division of Oncology Drug Products or the Oncologic Drugs Advisory Committee."

13. On or about December 9, 1997, FDA approved Evista for the prevention of osteoporosis in postmenopausal women.

14. As part of its initial NDA, ELI LILLY only submitted information that demonstrated the safety and efficacy of Evista for the prevention of osteoporosis in postmenopausal women. Evista was not approved for any therapeutic use other than the prevention of osteoporosis in postmenopausal women. Further, Evista was not, pursuant to 21 U.S.C. § 355(i), exempt from the prohibition of introducing into interstate commerce a new drug for medical indications beyond the conditions prescribed, recommended, or suggested in the approved labeling thereof.

15. Following the initial approval of a product label for Evista, ELI LILLY requested that FDA approve language in the product label with respect to Evista and newly diagnosed breast cancer. On November 24, 1998, FDA approved language in the "Effects on the Breast" subsection of the Clinical Pharmacology section of the approved product label for Evista. FDA approved language which stated: "Mammograms were routinely performed on an annual or biannual basis in all placebo-controlled clinical trials lasting at least 12 months. Independent

review has determined that 16 cases (raloxifene and placebo combined) represented newly-diagnosed invasive breast cancer. Among 7017 women randomized to raloxifene, there were 6 cases of invasive breast cancer per 14,605 person-years of follow-up (0.41 per 1000). Among 3368 women randomized to placebo there were 10 cases of invasive breast cancer per 6991 person-years of follow-up (1.43 per 1000). The effectiveness of raloxifene in reducing the risk of breast cancer has not yet been established."

16. In late September 1999, the FDA approved Evista for the *treatment* of osteoporosis in postmenopausal women.

17. Evista is only approved by FDA for the prevention and treatment of osteoporosis in postmenopausal women. These approved uses for Evista will be referred to throughout this Complaint as the "Approved Uses."

18. ELI LILLY has not filed a new NDA or supplemental NDA seeking FDA approval for any additional use for Evista.

19. ELI LILLY has been, and is now, engaged in the manufacturing, processing, packing, labeling, storing, and distributing in interstate commerce of Evista. ELI LILLY has also been, and is now, engaged in holding for sale Evista after shipment of Evista in interstate commerce.

20. Beginning as early as May 17, 1998 through May 11, 2000, Unapproved Uses for Evista promoted by ELI LILLY's Evista Brand Team (the group within ELI LILLY responsible for developing the marketing and promotional messages for Evista in the United States) and ELI LILLY sales representatives promoting Evista were the prevention and reduction in the risk of breast cancer and the reduction in the risk of cardiovascular disease. These Unapproved Uses for

Evista will be collectively referred to in paragraphs 2 - 36 of this Complaint as the "Unapproved Use(s)."

21. Following Evista's approval by the FDA for the prevention of osteoporosis in postmenopausal women, ELI LILLY confronted a marketing challenge. There were at least two established osteoporosis drugs being marketed by competitors of ELI LILLY. The medications frequently prescribed by doctors for the prevention or treatment of osteoporosis were Hormone Replacement Therapy ("HRT") and Fosamax. HRT was approved for, among other things, the prevention of osteoporosis. Fosamax was approved for the prevention and treatment of osteoporosis in postmenopausal women. ELI LILLY sought to demonstrate the reasons why doctors should prescribe its newly approved drug, Evista, over these other osteoporosis medications. Unlike the effects of Fosamax, which only operated to prevent and treat osteoporosis, ELI LILLY asserted that Evista had multiple benefits in addition to the prevention and treatment of osteoporosis.

22. In or about October 1998, ELI LILLY ran an advertisement in *Prevention Magazine* promoting Evista. The advertisement was approved by ELI LILLY's Evista Brand Team. The advertisement declared that Evista "Prevents osteoporosis . . . Lowers cholesterol . . . Addresses concerns about breast cancer."

23. On or about January 12, 1999, ELI LILLY received a Notice of Violation issued by the FDA, informing ELI LILLY that the advertisement violated the FDCA because it lacked fair balance, overstated Evista's benefits, presented an unsubstantiated safety claim, and minimized Evista's risk information. With respect to the overstatement of benefit, the FDA's Notice of Violation stated: "This advertisement is misleading because it overstates Evista's

benefits. By promoting 'Prevents osteoporosis . . . Lowers cholesterol . . . Addresses concerns about breast cancer' with equal prominence, this advertisement implies that Evista is indicated for a broader range of uses than supported by the product's labeling." In response to the Notice of Violation, ELI LILLY agreed in a letter to FDA not to run the advertisement again.

24. On December 11, 1998, ELI LILLY issued a press release titled "New Data to be Presented at Medical Meeting Show That Evista Reduces Breast Cancer and Other Risks Among Postmenopausal Women." The press release stated: "First Osteoporosis Preventive to Demonstrate Breast Cancer Risk Reductions in Clinical Trials."

25. On or about December 23, 1998, ELI LILLY was informed by FDA that ELI LILLY's press release was in violation of the FDCA. "This press release promotes Evista for unapproved new uses and is lacking in fair balance." In response to ELI LILLY's press release touting Evista's ability to reduce the incidence of newly diagnosed breast cancer, FDA's Notice of Violation explained:

> "DDMAC [FDA's Division of Drug Marketing and Communication] notes the recent labeling change which describes the number of cases of newly-diagnosed invasive breast cancer in patients treated with either Evista or placebo in clinical trials. However, the following statement was also added, 'The effectiveness of raloxifene in reducing the risk of breast cancer has not yet been established.' Despite, and, in fact, in disregard to this statement, Lilly promoted Evista for this use in direct contradiction to the APL [approved product label]. The press release is therefore inconsistent with the APL and promotes Evista for an unapproved new use. . . . Lilly should immediately discontinue the use of the press release and other promotional materials that contain the same or similar representations for Evista discussed above."

In response to the Notice of Violation, ELI LILLY stated in a letter to FDA that it had stopped disseminating the press release.

26. Before, during, and after ELI LILLY received these Notices of Violation from

FDA, ELI LILLY sales representatives promoting Evista promoted Evista in doctors' offices with the use of Evista's Three Combined Benefits message. The training materials for sales representatives stated that "Evista addresses three significant concerns of your postmenopausal patients: Evista builds bone. Evista for the prevention of postmenopausal osteoporosis. Evista addresses their concerns about breast cancer. Evista improves the lipid profile." This was the message promoted by ELI LILLY sales representatives promoting Evista. As part of this sales message, some ELI LILLY sales representatives specifically promoted Evista for its effectiveness in preventing and reducing the risk of breast cancer, and for reducing the risk of cardiovascular disease. By asserting that in addition to the prevention of osteoporosis, Evista prevents and reduces the risk of breast cancer and reduces the risk of cardiovascular disease, ELI LILLY created new intended uses for Evista.

27. Beginning as early as May 17, 1998 through May 11, 2000, ELI LILLY's Evista Brand Team and ELI LILLY sales representatives promoting Evista promoted the sale and use of Evista for Unapproved Uses in the Southern District of Indiana and elsewhere. Some ELI LILLY sales representatives met with doctors throughout the country and promoted Evista for the prevention and reduction in the risk of breast cancer and the reduction in the risk of cardiovascular disease.

28. On or about October 2, 1998, June 18, 1999, and March 2000, ELI LILLY's Evista Brand Team was provided with market research results from surveys of doctors who had recently been called upon by ELI LILLY sales representatives promoting Evista. When asked to recall the main messages or points that were communicated about Evista by ELI LILLY sales representatives in their most recent call, approximately one quarter of the doctors surveyed in

each of the three studies recalled receiving the message that Evista "may reduce/reduces the risk of breast cancer."

29. Beginning in or about the second and third quarters of 1998, some ELI LILLY sales representatives promoting Evista were encouraged to send unsolicited medical letters to doctors on their sales routes promoting Evista for the reduction in the risk of breast cancer.

30. On or about October 9-11, 1998, and October 22-24, 1999, ELI LILLY's Evista Brand Team organized consultant meetings for physicians who prescribed Evista. Among the presentations made to the physicians were "Evista and Markers of Cardiovascular Risk" and "Estrogens, Anti-Estrogens and SERMs: Impact on Breast Cancer Incidence and Implications For Prevention." During these presentations, Unapproved Uses of Evista were discussed.

31. In or about June 1999, some ELI LILLY sales representatives promoting Evista were trained to use an article reprinted from the Journal of the American Medical Association ("JAMA") to promote Evista for the prevention or reduction in risk of breast cancer, an Unapproved Use. ELI LILLY sales representatives were provided by ELI LILLY with copies of the JAMA reprint entitled: "The Effect of Raloxifene on Risk of Breast Cancer in Postmenopausal Women: Results From the MORE Randomized Trial." In training ELI LILLY sales representatives on how to present this reprint to doctors, some ELI LILLY sales representatives promoting Evista were instructed to hide the disclosure page which noted, among other things, that "All of the authors were either employees or paid consultants of Eli Lilly at the time this article was written," and "the prescribing information provides that 'The effectiveness of raloxifene in reducing the risk of breast cancer has not yet been established.'" In addition, these ELI LILLY sales representatives were trained to use the reprint to highlight key results of

Evista and thereby promote Evista to doctors for an Unapproved Use.

32. In or about August 1999, ELI LILLY's Market Research's Tech Core group calculated the incremental new prescriptions for doctors who attended Evista Advisory Board meetings in October and November, 1998, and for doctors who received continuing medical education audiotapes between February and April 1999. The Evista Advisory Board meetings included discussion of Unapproved Uses for Evista. The author of the study concluded "The best interventions in order of average share shift are: Advisory Boards . . . Teleconferences . . . Audiotapes." By measuring and analyzing incremental new prescriptions for doctors who attended Advisory Board meetings or were provided with audiotapes purporting to be continuing medical education, ELI LILLY was using these "interventions" as tools to promote and sell Evista.

33. Evista distributed by ELI LILLY was misbranded within the meaning of 21 U.S.C. § 331(a), in that the labeling of Evista did not bear adequate directions for use for all of the intended uses of the drug, specifically for use in preventing or reducing the risk of breast cancer or reducing the risk of cardiovascular disease. Because Evista is not approved for the prevention or reduction in the risk of breast cancer and the reduction in the risk of cardiovascular disease, Evista's labeling did not bear adequate directions for the use for these intended uses, and its labeling did not have any directions for these intended uses. Thus, the marketing of Evista for these Unapproved Uses without bearing adequate directions for use violated the law.

34. ELI LILLY violated the FDCA, 21 U.S.C. § 331(a), by causing the introduction into interstate commerce of Evista, a human drug within the meaning of 21 U.S.C. § 321(g), that was misbranded within the meaning of 21 U.S.C. § 352(f)(1), as set forth in Paragraphs 1 - 33.

35. ELI LILLY violated the FDCA, 21 U.S.C. § 331(k), by causing the misbranding of Evista, a human drug within the meaning of 21 U.S.C. § 321(g), while Evista and any of its components were held for sale after shipment in interstate commerce, as set forth in Paragraphs 1 - 33.

36. Plaintiff is informed and believes that, unless enjoined by this Court, there is a reasonable chance of recurring violations by ELI LILLY of 21 U.S.C. §§ 331(a) and 331(k) in the manner herein alleged.

WHEREFORE, PLAINTIFF PRAYS:

1. That ELI LILLY, and all of its subsidiaries, divisions, and controlled joint ventures, and each and all of their officers, directors, agents, employees, attorneys, and those persons in active concert and participation with them or any of them shall:

a. be permanently enjoined from violating the FDCA, 21 U.S.C. § 331(a), by directly or indirectly causing the introduction or delivery for introduction into interstate commerce of Evista, a human drug within the meaning of 21 U.S.C. § 321(g), that is misbranded within the meaning of 21 U.S.C. § 352(f)(1), in that the labeling of the drug does not bear adequate directions for use in preventing or reducing the risk of breast cancer, reducing the risk of cardiovascular disease, or for any other unapproved use, unless and until it has been authorized to do so by the FDA by the approval of a supplement to the NDA for Evista;

b. be permanently enjoined from violating the FDCA, 21 U.S.C. § 331(k), by directly or indirectly causing Evista, a human drug within the meaning of 21 U.S.C. § 321(g), to be misbranded within the meaning of 21 U.S.C. § 352(f)(1), in that the labeling of the drug does not bear adequate directions for use in preventing or reducing the risk of breast cancer, reducing

the risk of cardiovascular disease, or for any other unapproved use, while such drug is held for sale after shipment of it or any of its components in interstate commerce, unless and until it has been authorized to do so by the FDA by the approval of a supplement to the NDA for Evista; and

c. be permanently enjoined from directly or indirectly promoting Evista for use in preventing or reducing the risk of breast cancer, reducing the risk of cardiovascular disease, or for any other unapproved use in a manner that violates the FDCA, 21 U.S.C. § 301 et seq., unless and until it has been authorized to do so by the FDA by the approval of a supplement to the NDA for Evista.

2. That FDA be authorized pursuant to this injunction to review ELI LILLY's compliance with the terms of this injunction, with the non-legal costs of such review to be borne by ELI LILLY at the rates prevailing at the time the reviewing is performed.

3. That ELI LILLY be ordered to disgorge profits of twenty-four million dollars ($24,000,000) from its sale of misbranded Evista from May 17, 1998 through May 11, 2000.

4. That this Court grant such other and further relief as it deems just and proper.

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